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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,785	03/22/2001	Ira J. Fox	UNMC -0032	5547

7590 03/21/2006
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EXAMINER

LI, QIAN JANICE

ART UNIT PAPER NUMBER

1633

DATE MAILED: 03/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/816,785

Applicant(s)

FOX ET AL.

Examiner

Q. Janice Li, M.D.

Art Unit

1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 December 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 8, 14, 16-22 and 25 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 8, 14, 16-22 and 25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The amendment and response filed 12/22/05 have been entered. Claims 8, 14, 16-22, and 25 have been amended. Claims 8, 14, 16-22, 25 are under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims and a clear indication of deposit under the terms of the Budapest Treaty will not be reiterated. The arguments in 12/22/05 response would be addressed to the extent that they apply to current rejection.

Claim Objections

Claim 25 is objected to because the word "isolated" should be inserted before "reverse-immortalized". The claim reads on a reverse-immortalized hepatocyte implanted and integrated into a human subject, and thus the claim as written encompasses a human subject, would have to be rejected under **35 USC § 101** if the word "isolated" is not included. Appropriate correction is expected.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 8, 14, 16-22, 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are vague and indefinite because of the claim recitation, "wherein said hepatocyte (cell line) is entrapped in a matrix disposed to receive cells for transplantation". It is unclear whether the phrase merely describes the location of the hepatocyte or claiming a composition comprising isolated hepatocytes and a matrix, and thus the metes and bounds of the claims are uncertain.

Likewise, applicant indicates that they would deposit the cell line under the term of the Budapest Treaty upon allowance of claim 22. However, it is now unclear whether the deposit would include a biomatrix, if so, how the cells being propagated. Thus the metes and bounds of the claims are unclear.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The prior rejection of Claims 14, and 25 under 35 U.S.C. 102(e) as being anticipated by or in the alternative under 35 U.S.C. 103(a) as obvious over *Jakobovits et al* (USP 6,130,364), is withdrawn, because the hepatocytes of the transgenic mouse taught by the cited patent contains one loxP site, not the neo-R gene and a promoter derived from MoMLV. The antibody producing cells, not hepatocytes of the mouse, contain all of the structure on the list.

Claim Rejections - 35 USC § 103

Claims 8, 14, 16-20, 25 stand rejected modified under 35 U.S.C. 103(a) as being unpatentable over *Nakamura et al* (Transplant 1996;63:1541-7, IDS), in view of *Anderson* (USP 5,629,159, IDS), for reasons of record and following.

With regard to rejections relied on *Nakamura et al*, Applicants argue the above references neither alone or in combination teach reverse-immortalized hepatocytes entrapped in a matrix for transplantation. *Nakamura* teaches engraftment of free conditionally immortalized hepatocytes.

In response, claims as written remain drawn to isolated, immortalized or reverse-immortalized hepatocytes, the combined teachings in the art would generate cells that

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meet structural limitation of the claimed cells. The novelty of the cell is determined by the structure of the cell regardless where the cell is located or entrapped.

Accordingly, the rejection stands.

Claim 21 stands rejected under 35 U.S.C. 103(a) as being unpatentable over *Nakamura et al* (Transplant 1996;63:1541-7, IDS), in view of *Anderson* (USP 5,629,159, IDS), as applied to Claims 8, 14, 16-20, 25 above, and further in view of *Adams et al* (Proc Natl Acad Sci U S A. 1992 Oct 1;89(19):8981-5), for reasons of record and set forth *supra*.

The follow rejection applies when claims read on, or being amended to read on a composition comprises both hepatocytes and a biomatrix.

Claims 8, 14, 16-20, 25 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Nakamura et al* (Transplant 1996;63:1541-7, IDS), in view of *Anderson* (USP 5,629,159, IDS), and *Edge et al* (USP 6,610,288).

Nakamura et al teach conditionally immortalized hepatocytes transfected with a replication-defective retroviral vector encoding a thermolabile mutant SV40 T antigen, which confers a reversible immortalization based on the transgene permissive temperature. *Nakamura et al* go on to teach that the transduced hepatocytes significantly improve the survival of rats with acute liver failure (e.g. abstract and fig. 1), and the strategy provides a remedy for the shortage of liver donor in humans (1st

paragraph, page 1541, column 2). *Nakamura et al* go on to teach development of this technology for clinical use would require production of hepatocyte cell lines with tighter regulation on the expression of the transforming gene than a simple temperature-sensitive mutation, and suggested to use site-specific recombination to excise the transforming gene from a cell line prior to transplantation (last paragraph, page 1546). The teaching of *Nakamura et al* differs from instant invention in that it does not physically use the site-specific recombinase for conditional immortalizing the hepatocytes.

Anderson supplemented the teaching of *Nakamura et al* by illustrating the details concerning how to use site-specific recombinase for immortalizing and then disimmortalizing mammalian cells. *Anderson* teaches that the exogenous nucleic acid used in gene therapy is often carried by the cells of a patient's own, and for the purpose of expansion and genetic manipulation, these cells are often immortalized, which may be oncogenic when transplanted back to the patient (Introduction). Accordingly the invention provided methods and cells that may be disimmortalized. *Anderson* discloses a population of immortalized primary murine fibroblast cells transformed with a DNA construct integrated into the genome of said cell, wherein the construct comprises two recombinase target sites (loxP) flanking an oncogene v-myc, (e.g. claim 1, and column 15, lines 11-17), which confers immortalization to said cell; wherein the construct further comprises a selectable marker (e.g. claim 2), and a suicide gene (HPV-tk, column 5, lines 25-38). *Anderson* teaches the immortalization is reversible by introducing a Cre recombinase expression construct into said cell (column 15, lines 61-63, and claims 10-

18) and remaining cells containing the oncogene can be destroyed by exposure to gancyclovir. *Anderson* goes on to teach that suitable cells for practicing the claimed invention include any cell type that does not produce a recombinase recognizing the target sequence in the construct, wherein the cells may be obtained from vertebrate, mammalian, and preferably human cells (column 12, lines 32-44). The disclosure of *Anderson* differs from the claimed invention in that he does not particularly name or transduce hepatocytes, however, such was suggested by *Nakamura et al.*

The combined teaching of *Nakamura et al* in view of *Anderson et al* does not teach that incorporate hepatocytes with a matrix for transplantation. However, *Edge et al* supplement the above teach by establishing it was well known in the art before the effective filing date that hepatocytes could be transplanted to a subject either in a cell suspension, or embedded in a support matrix (column 18, lines 37-39), wherein the matrices could be synthetic or naturally biodegradable, which provide support and protection for hepatocytes *in vivo* (column 18, lines 55-64).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by *Nakamura et al* in view of *Anderson*, with that of *Edge et al* by embedding the reverse-immortalized hepatocytes in a biodegradable matrix with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the support and protection provided by the matrices would enhance the engraftment of hepatocytes implant. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 21 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Nakamura et al* (Transplant 1996;63:1541-7, IDS), in view of *Anderson* (USP 5,629,159, IDS), and *Edge et al* (USP 6,610,288) as applied to Claims 8, 14, 16-20, 25 above, and further in view of *Adams et al* (Proc Natl Acad Sci U S A. 1992 Oct 1;89(19):8981-5), for reasons of record and set forth *supra*.

Conclusion

No claim is allowed. Claim 22 is free of cited art of record, but it is subject to other rejection.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Dave T. Nguyen** can be reached on 571-272-0731. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **William Phillips**, whose telephone number is (571) 272-0548.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

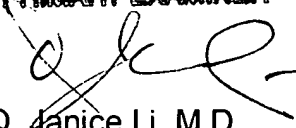
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Q. JANICE LI, M.D.
PRIMARY EXAMINER



Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL

March 17, 2006